REMARKS

FORMAL MATTERS:

Claims 31-79 are pending in this application, and under examination. No amendment is made to the claims or any other part of the disclosure in this Response.

Claims 31-40, 46-48, 52, 54-60, 63-67, 69, 70, 74, 75 and 77-79 stand rejected as obvious with respect to cited references by Jadus et al., and Kimura et al.

Applicants acknowledge with gratitude withdrawal of all other rejections previously made under 37 CFR §§ 112, 102, and 103.

ALLOWABLE SUBJECT MATTER

Claims 41-45, 49-51, 53, 61, 62, 68, 71-73 and 76 are objected to as depending from a rejected base claim, but are otherwise not rejected. Applicants note that claim 70 was indicated as rejected on the cover sheet, but no rejection was applied in the text of the Office Action. Claim 70 sets out a limitation similar to that of claim 41. Claim 41 is indicated as being objected to but not rejected in view of the cited art. Thus, applicants believe that claim 70 should likewise be free of the prior art.

INTERVIEW SUMMARY :

Applicants are grateful to Examiner Christopher Yaen and Examiner Gary Nickol for the courtesy of a cordial and helpful interview on September 2, 2004 with Carol Francis, attorney of record, and Michael Schiff, representative of the licensee.

Prior art rejections over the Jadus and Kimura references were discussed, and possible arguments to overcome the rejections were presented. Applicants understand that the Examiners consider Kimura et al. to be more problematic, since this paper reports experiments done with live animals, whereas Jadus et al. report only tissue culture experiments.

The discussion during the interview is reflected in the comments presented here, and are believed to place the application in condition for allowance.

§102(a) AND §103(a) – THE JADUS REFERENCE

The rejection of claims 31-33, 35, 36, 38, 40, 46-50, 52-60, 63-65, 67, 69, 72-73, 75-78 and 79 under 35 USC §§ 102(a) and/or 103(a) as being not novel and/or obvious in view of Jadus et al., Blood 87:5232-5241, 1996 was maintained for reasons of record. Previous Office Actions have inferred that since some of the cells reported in the Jadus article express the membrane form of M-CSF, it would be obvious to use them according to the methods claimed in this patent application for human therapy.

Applicants respectfully disagree. The M-CSF expressing cells are used by Jadus as targets in assays to study the cytotoxicity of primed macrophages. The assays are conducted entirely *in vitro*. There is no suggestion that any of the components reported in the paper be used for human therapy. Even if a reader were somehow inspired to adapt the article for clinical practice, the therapies to be drawn from the paper would either be administration of stimulated macrophages, or gene therapy of patients own tumor cells to express M-CSF. The reader will not be led to administer cytokine-expressing cells (especially allogeneic or inactivated cells) as part of a cancer therapy — except by way of hindsight from the present disclosure.

As discussed during the interview, this argument dismisses the Jadus article as affecting the patentability of the claimed invention. Applicants maintain their position that the article does not qualify as a § 102(a) reference for reasons explained previously.

Withdrawal of this rejection is respectfully requested.

§103(a) – THE KIMURA REFERENCE WITH DICK ET AL.

Claims 31-34, 35-36, 38, 40, 46-50, 52-60, 63-65, 67, 69, 72-73 and 75-78 in the application stand rejected under 35 USC § 103(a) as being obvious over Kimura et al., Exp. Hematol. 24:360-363, 1996.

Applicants are su rprised that this reference has been cited against the application a second time. Kimura was cited under § 102(a) in the first Office Action on the merits, dated October 3, 2002. Applicants discussed this reference with the Examiners in an interview held on February 27, 2003, and responded to the Office Action on March 11, 2003. As a consequence, the rejection with respect to Kimura et al. was withdrawn in the Office Action that followed on June 3, 2003.

The Kimura reference has now been cited against the application again, on substantially the same basis. The Office Action asserts that all the limitations of the claimed invention can be found in the

reference, except for the use of the compositions in humans. It suggests that the following actions required in the method claims presented here are described in the reference:

a) The cytokine expressing cells in the composition synthesize both secreted and membrane forms of M-CSF;
b) The cytokine expressing cells in the composition bear tumor-associated antigen; and
c) Administration of the composition to the animals generated a tumor-specific immune response in view of Kimura's observation that when mice having M-CSF-expressing tumor cells were challenged with L1210 cells, the mice survived (see abstract).

A second reference by Dick et al. (Cancer Surv. 15:161, 1992) is cited as standing for the proposition that mouse models are "relatively" predictive and can be "correlative" to clinical outcome. Thus (the argument goes), someone skilled in the art reading the Kimura reference would be motivated to do the same experiment with human subjects, and would inherently achieve all the requirements of the method claimed in this application.

Applicants respectfully disagree. The Kimura model differs substantially from how the specification indicates the claimed invention should be used to treat cancer patients.

Specifically, Kimura injected *live cancer cells* into *naïve* (previously healthy) experimental animals. The administered cells normally grow into a lethal tumor in the animals. But when the cells are caused to express M-CSF, the animals have an improved frequency of survival. The authors attribute this to a tumoricidal activity of M-CSF (page 362, Col. 1 ¶ 2), and suggest the use of M-CSF for gene therapy of cancer patients (page 362, Col. 2 ¶ 2). Nothing is stated about the benefits of using a gene encoding membrane-associated M-CSF. In fact, the article directs the attention of the reader to the *secreted form* of M-CSF:

> The M-CSF content *in the conditioned medium* of the transfected cells was measured by enzyme-linked immunosorbent assay (ELISA).
> – Kimura et al., p. 360 col. 2 ¶ 3 (emphasis added).

In contrast, the present patent disclosure teaches treatment methods that involve the administration of a cellular composition. The composition comprises cells that express a cytokine, and acts as an effective therapeutic agent for treating a patient for a *preexisting tumor*. Effectiveness of the

treatment correlates with the level of membrane expression of membrane cytokine (page 62, line 25 to page 63, line 2). Evidence of a tumor-specific immune response was obtained by showing that protection could be transferred from one animal to another by way of a lymphocyte-containing cell population (page 63, lines 11-17).

As set out in MPEP §2143, in order to establish a prima facie case of obviousness, three basic criteria must be met.

1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
2) There must be a reasonable expectation of success.
3) The prior art reference, or references when combined, must teach or suggest all the claim limitations.

All three criteria must be met. If any one of these three criteria is not met, a prima facie case of obviousness has not been established.

There are at least two ways in which the Office has failed to establish that the invention claimed here is *prima facie* obvious with respect to the Kimura and Dick references.

First the Office has not shown that *each and every claim limitation* is taught or suggested in the cited prior art.

Independent claims 31, 50, and 79 and claims dependent thereon, as well as dependent claims 72 and 73 require that the cells having a membrane cytokine be *inactivated to prevent proliferation.* This patent application describes how the cells can be irradiated with a titrated dose to prevent proliferation, but still synthesize cytokine (page 47, line 15 to page 48, line 24; page 51, lines 14-22; page 53, lines 21-25; page 59, lines 14-23). This allows the cells to retain their function of stimulating a response, without posing an additional tumorigenic risk to the treated subject.

This feature is not taught or suggested by Kimura. Instead Kimura teaches use of *live (tumorigenic) cells*. There is no suggestion in the article that the cells can or should be inactivated in such a way that they are unable to proliferate, but still remain viable and continue to synthesize the recombinant cytokine. The secondary reference of Dick fails to provide this missing element. Applicants

note that dependent claims that recite particular ways to inactivate cells are not rejected as being obvious over Kimura and Dick (see, e. g. , claims 44 and 45).

Clearly, the experiments done in the Kimura reference cannot be directly adapted to human therapy. No competent physician would contemplate injecting her patients with live and potentially lethal cancer cells. Of course, in order to decide how to adapt a § 103 reference for human treatment, it is improper to do so with the benefit of hindsight from the subject patent application. It is also improper to draw adaptations from features that are inherent in the reference, but not disclosed as being present.

Second, Kimura provides insufficient guidance to the ordinarily skilled artisan adapting the teachings of this reference to human treatment to incorporate use of *cells* having the membrane form of M-CSF. Kimura does not indicate that his cells even make the membrane form.

In fact, Kimura takes the reader in quite a different direction.

> Our findings imply that M-CSF cDNA is a candidate gene for use in *gene therapy* of lymphoid leukemia.
>
> — Kimura et al., page 362, Col. 1 ¶ 2, emphasis added.

Kimura thus explicitly indicates that the animal experiments are only a model in which the patient's *own tumor* is treated so as to cause it to express the M-CSF itself. This presumably would be done by administering into the tumor a suitable expression vector encoding human M-CSF — for which an exact recipe is given on page 360, Col. 2, ¶ 3.

Adaptation of the teaching of Kimura in view of Dick thus would not lead to the methods of the claimed invention. Instead, a therapeutic method reasonably drawn from the Kimura reference would use a gene construct — *not even comprising cells!* The invention claimed here clearly cannot be drawn from the reference except through the benefit of hindsight from the present disclosure.

The Office Action has also failed to establish a *prima facie* case of obviousness is that it has overlooked several features of the claimed method that are explicitly required, and which further distinguish the claims from anything taught or suggested by Kimura.

Claim 64 and its dependents are further distinguished from anything suggested by Kimura et al., because the claims require that the cell expressing the cytokine *be allogeneic* to the treated subject. It is virtually certain that the L1210 cells used in the Kimura article were syngeneic to the animals they were

administered to, because they grew to form a tumor of lethal size without being rejected. Transfecting the cells with M-CSF apparently affected the viability or proliferation of the cells themselves in vivo.

In contrast, this patent application proposes that cytokine expressing cells be administered to the patient *so as to recruit the host's immune system,* which in turn generates a response against the tumor as a bystander antigen. According to this rationale, the cytokine-expressing cell can be *allogeneic,* since it need not persist at the site once the host's own immune system has been activated. Allogeneic cells that are third-party (off-the-shelf) pre-engineered components facilitates the treatment methods of this invention.

In summary, the invention claimed here is distinguished from anything taught or suggested by Kimura et al., because adaptation of the Kimura experiments for human therapy will cause the treatment method to lose inherent properties relied upon in the Office Action. Furthermore, the claims all require one or more additional features which are not taught or suggested in the reference

Applicants do not concede that this publication is valid prior art under § 102(a). Applicants also do not concede that the article describes any of the features recited in the dependent claims in this application. These points need not be addressed further, because the arguments presented already are sufficient to overcome the rejection.

Withdrawal of this rejection is respectfully requested.

REQUEST FOR FURTHER INTERVIEW

Applicants submit that all of the claims are in condition for allowance, which action is requested.

In the event the Office determines that there are patentability matters still to be resolved, applicants hereby request a further interview with the Examiner so as to expedite prosecution of the application. It would be of considerable assistance to the owner and the licensee to have this patent issue, so as to promote commercialization of the invention for the benefit of cancer patients.

CONCLUSION

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-001DIV2.

Respectfully submitted,
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